Accepted Autor Manuscript. Published in final edited version in Epilepsy & Behavior 2019. Publisher's DOI: https://doi.org/10.1016/j.yebeh.2019.106466

Intravenous antiepileptic drugs in adults with benzodiazepine-resistant convulsive status epilepticus: a systematic review and network meta-analysis

Francesco Brigo[1,2], Cinzia Del Giovane[3], Raffaele Nardone[1,4], Eugen Trinka[4,5], Simona Lattanzi[6]

[1]Division of Neurology, "Franz Tappeiner" Hospital, Merano, Bolzano, Italy

[2]Department of Neuroscience, Biomedicine and Movement Science, University of Verona, Verona, Italy

[3]Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland

[4]Department of Neurology, Christian Doppler Klinik, University Hospital Paracelsus Medical University, Salzburg, Austria.

[5]Institute of Public Health, Medical Decision Making and Health Technology Assessment, University for Health Sciences, Medical Informatics and Technology, UMIT, Hall in Tyrol, Austria.

[6]Neurological Clinic, Department of Experimental and Clinical Medicine, Marche Polytechnic University, Ancona, Italy

Corresponding Author: Francesco Brigo, Department of Neuroscience, Biomedicine and Movement, University of Verona, Italy. Piazzale L.A. Scuro, 10 - 37134 Verona, Italy.
Tel.: +390458124174; fax +390458124873
E-mail: dr.francescobrigo@gmail.com

Abstract

Aim: The aim of this study was to estimate the comparative efficacy and safety of antiepileptic drugs (AEDs) in adults with benzodiazepine-resistant convulsive status epilepticus (SE).

Methods: MEDLINE, CENTRAL, ClinicalTrials.gov and Opengrey.eu were searched (from inception to 3rd April, 2018) for randomized controlled trials (RCTs) of AEDs used intravenously to treat benzodiazepine-resistant SE in adults. Efficacy outcomes were: SE cessation within 1 hour from drug administration; seizure freedom at 24 hours. Safety outcomes were: respiratory depression; hypotension. Effect sizes were estimated by network meta-analyses within a frequentist framework. The hierarchy of competing interventions was established using the surface under the cumulative ranking curve (SUCRA) and mean ranks.

Results: Five RCTs were considered, involving 349 patients. Included interventions were valproate (VPA; 20-30 mg/kg), phenytoin (PHT; 20 mg/kg), diazepam (DZP; 0.2 mg/kg, then 4 mg/h), phenobarbital (PHB; 20 mg/kg, then 100 mg every 6 h), lacosamide (LCM; 400 mg) and levetiracetam (LEV; 20 mg/kg). PHB was superior to PHT, VPA, DZP, LEV and LCM with respect to SE cessation and performed better than VPA, DZP and LCM in the achievement of seizure freedom at 24 hours. No differences were noted between drugs in the occurrence of respiratory depression and hypotension. According to SUCRA, PHB had the greatest probabilities of being best in the achievement of SE control and seizure freedom, whereas VPA and LCM ranked best for the safety outcomes.

Conclusions: Our study suggests that high-dose PHB is effective in controlling SE and preventing seizure recurrence, and LCM and VPA could be better tolerated options. Further head-to-head comparative studies are strongly required to provide more definitive evidence.

Key words:

Efficacy

Network Meta-Analysis

Safety

Status epilepticus

Introduction

Status epilepticus (SE) is as a condition "resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally, prolonged seizures" [1]. It is a medical and neurological emergency, with long-term consequences including "neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures" [1]. More specifically, convulsive SE is a life-threatening neurological emergency, with a mortality reaching 20% [2]. The pharmacological treatment of convulsive SE relies on the use of benzodiazepines as first-line agents. In approximately 30-40% of cases, SE can not be adequately controlled by benzodiazepines and requires the intravenous (IV) administration of antiepileptic drugs (AEDs). The most commonly used agents include phenytoin (PHT), phenobarbital (PHB), valproate (VPA), levetiracetam (LEV), and lacosamide (LCM) [3-5].

To provide useful clinical guidance, it would be important to have data on their comparative efficacy and safety. So far, however, very few randomized controlled trials (RCTs) have been conducted and the amount of information from direct head-to-head comparisons is very limited [6]. The aim of this study was, hence, to systematically and critically appraise the extant RCTs of AEDs used to treat benzodiazepine-resistant convulsive SE in adults, and estimate their comparative efficacy and safety by means of a network meta-analysis.

Methods

The study results were reported according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for network meta-analyses [7] (Appendix I, supplementary material). The review protocol was not previously registered.

We included RTCs directly comparing any AED administered IV versus any AED as second-line treatment for convulsive SE continuing despite benzodiazepine administration (benzodiazepine-resistant SE) in adult patients (≥15 years).

The following electronic databases and data sources were systematically searched:

1.MEDLINE (January 1966–3rd April 2018), accessed through PubMed;

2.Cochrane Central Register of Controlled Trials (CENTRAL; accessed 3rd April 2018);

3.ClinicalTrials.gov (available at: https://clinicaltrials.gov/; accessed 3rd April 2018);

4. Opengrey.eu (available at: www.opengrey.eu; accessed 3rd April 2018)

Search strategy adopted for all the above mentioned databases is reported in Appendix II (supplementary material). All resulting titles and abstracts were evaluated, and any relevant article was considered. No language restrictions were adopted. We excluded all RCTs administering IV AEDs either simultaneously or immediately after benzodiazepines, hence without demonstrating refractoriness of SE to benzodiazepines [5].

Retrieved articles were independently assessed for inclusion by two review authors (FB, RN); any disagreement was resolved through discussion. The methodological quality of all included studies and the risk of bias were assessed as outlined in the Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0 [updated March 2011] [8].

The following trial data were independently extracted by two review authors (FB, RN): main study author and age of publication; country; definition of SE; total number, age, and sex of participants for each treatment group; history of previous seizures; type of SE; SE duration; etiology of SE; details of benzodiazepine administration; details of IV AEDs used as second-line agents for SE (tested drug and comparator). The following efficacy outcomes were considered: cessation of SE following IV AED administration within 1 hour from drug administration; seizure freedom at 24 hours. The following safety outcomes were assessed: respiratory depression; hypotension. The intent-to-treat population data were used for the analyses. First, we did pairwise meta-analyses for all outcomes, using a fixed-effects model. Second, we performed network meta-analyses within a frequentist framework assuming equal heterogeneity parameter τ across all comparisons [9]. It is appropriate to use NMA if the assumption of transitivity (distributions of the potential effect modifiers, like study and patient-level covariates, are balanced across all pairwise comparisons) can be defended [10]. We assessed the transitivity assumption looking at the similarities of studies in each comparison. As not closed loops were present in each network of treatments, we were not able to assess the agreement between direct and indirect evidence for a specific comparison (consistency assumption) [11]. Effect sizes were estimated as odds ratios (ORs) with their 95% confidence intervals (CIs). The hierarchy of competing interventions was established using the surface under the cumulative ranking curve (SUCRA) and mean ranks [12]. Data analysis was performed using STATA/IC 13.1 statistical package (StataCorp LP, College Station, TX, USA).

Results

A total of 659 records was identified by database and trial registers searching (303 MEDLINE, 285 CENTRAL, 21 Opengrey.eu, and 50 ClinicalTrials.gov). After excluding duplicates and reading title and abstracts, 6 RCTs were initially included [13-18]. One study comparing VPA with PHT [13] was eventually excluded, as it provided data on SE control within 7 days of administration and this time cut-off was considered to be too long to be clinically meaningful.

Hence, five RCTs were included in our review, involving 349 patients (Fig.1). Following comparisons were included: IV VPA versus PHT [14], IV LEV versus PHT [15], IV LCM versus VPA [16], diazepam (DZP) versus VPA [17], and PHB versus VPA 30 [18]. Details of included interventions (dosages and rate of drug administration) and characteristics of the included trials are reported in Table 1. Characteristics of study participants are summarized in Table 2. All included studies were conducted in patients with convulsive SE (mostly with generalized convulsive SE); etiology and SE duration differed remarkably across studies. The clinical definitions of SE adopted were homogeneous between different studies, as well as dosages of benzodiazepines administered as first-line treatment. The risks of bias are detailed in Table e-1. All studies were not blinded or did not provide details on blinding therefore at high risk of performance bias. The risk of detection bias was deemed to be low, since outcome measurement (cessation of convulsive SE) was unlikely to be influenced by lack of blinding.

Figure 2 shows the network plots of treatment comparisons for the efficacy and safety outcomes. Results of the pairwise meta-analyses are reported in Table e-2. The only significant differences were the higher proportions of SE cessation (OR: 5.36; 95% CI: 1.87-15.36; p=0.002) and seizure freedom at 24 hours (OR: 7.07; 95% CI: 2.52-19.86) in patients taking PHB compared to VPA.

Results of the network meta-analyses of efficacy and safety outcomes are shown in Figure 3. PHB was superior to PHT, VPA, DZP, LEV and LCM with respect to SE cessation and performed better than VPA, DZP and LCM in the achievement of seizure freedom at 24 hours. No differences were noted between drugs in the occurrence of respiratory depression and hypotension. The comparative effects of all treatments were ranked using SUCRA values (Table 3 and Appendix III). According to SUCRA, PHB had the greatest probabilities of being best in the achievement of SE control and seizure freedom, whereas VPA and LCM had the greatest likelihood ranking best for the safety outcomes.

Discussion

The present study represents the first attempt to perform a systematic analysis of RCTs selectively conducted in adults with convulsive SE in whom refractoriness to benzodiazepines was clearly reported. The rather strict inclusion criteria were chosen to reduce clinical and methodological heterogeneity, with the ultimate aim to provide an informative, possibly unbiased, qualitative and quantitative synthesis of the currently available evidence.

Direct comparisons did not find a difference in efficacy between most AEDs, probably because of the small number of patients included and the consequent risk of false negative results due to statistical error type II. Although it is likely that a difference in efficacy between the AEDs exists, one cannot exclude that such difference is of small magnitude and requires a larger number of patients to be demonstrated [19,20]. The only direct comparison showing a significant difference in efficacy was the one between PHB and VPA; however, this is likely attributable to the high dose of PHB used in the RCT [18].

Network meta-analyses are not substitutes for clinical trials directly comparing two or more drugs but may provide some evidence of their relative efficacy and safety [21,22]. The current network meta-analysis of RCTS in benzodiazepine-resistant convulsive SE could offer useful information about the hierarchy of competing interventions. Remarkably, PHB resulted the most effective treatment in controlling SE, whereas LCM and VPA ranked best for the safety outcomes.

The findings of the present study should be interpreted with caution considering the limited number of included studies, their small sample sizes and clinical heterogeneity in SE duration and etiology. Differences in dosages should be also taken into account in interpreting the results. The high relative efficacy of PHB found in indirect comparisons, both in terms of SE cessation within 1 hour from drug administration and lack of SE relapse at 24 hours, is likely to reflect the high dose of PHB [18]. Of note, the PHB dose used in this RCT (20 mg/kg, followed by 100 mg every 6 hours) was much higher than the maximal dose (15 mg/kg, given as single dose) recommended by the recent evidence-based guideline of the American Epilepsy Society for the treatment of convulsive SE in children and adults [23]. In addition, both VPA and LEV were used at dosages much lower (respectively 20-30 mg/kg and 20 mg/kg) than those reported by the American Epilepsy Society, which recommends to

administer VPA at 40 mg/kg (max. 3000 mg/dose; single dose) and LEV at 60 mg/kg (max. 4500 mg/dose; single dose) [23]. It is therefore likely that the dosages adopted in the included RCTs were too low to detect a significant difference with the active comparator, possibly reducing their efficacy.

Phenytoin ranked worst in the likelihood of reaching SE cessation. This probably reflects the need to administer this drug not exceeding the maximum infusion rate of 50 mg/min to prevent hypotension and cardiac arrhythmia [3,4]. The related drawback is a long infusion time (administering PHT 18–20 mg/kg at 50 mg/min in an adult weighing 70 kg takes approximately 0.5 h), which might result in lower seizure control [5,24].

Although no clear-cut differences were found across treatments in the safety outcomes, VPA and LCM were associated with the lowest likelihood to develop respiratory depression and hypotension and suggested to be among the better tolerated options. Not surprisingly, PHB at such high dosage ranked as the worst treatment with respect to both the safety endpoints. Unfortunately, comparisons between different dosages of AEDs to adjust results for dose-effects were not feasible due to the very small number of studies, each of them evaluating only one single dose of tested drugs. Furthermore, to date there is no information on equi-effective doses of AEDs for the treatment of SE, or – more generally – for the treatment of epilepsy [22,25].

A prior meta-analysis comparing the efficacy of five AEDs in benzodiazepine-resistant convulsive SE suggested that VPA, PHB, and LEV can all be used in this condition; the evidence was not considered to be sufficiently high to support the use of PHT, whereas no enough data were found on LCM [26]. Notably, the results were limited by methodological heterogeneity due to the inclusion of both retrospective and prospective controlled trials, studies conducted in children and adults, and adopting different definitions of treatment response (SE cessation within time frames ranging from 3 minutes up to 48 hours) [27].

The present study confirms that the evidence supporting the use of specific AEDs for the treatment of benzodiazepine-resistant convulsive SE in adults relies on few RCTs with a small number of participants. This emphasizes the need for high-quality and adequately powered RCTs to establish the individual role of AEDs in the management of benzodiazepine-resistant SE and evaluate whether any of them deserves to be considered as the best agent.

To date, there are no high-quality, evidence-based data to prefer the use of one AED over another in the treatment of benzodiazepine-resistant convulsive SE, and further head-to-

head comparative studies are urgently needed. The Established Status Epilepticus Treatment Trial (ESETT; NCT01960075), funded by the National Institute of Neurological Disorders and Stroke, is a large ongoing trial aimed at comparing efficacy and safety of fosphenytoin, VPA and LEV in benzodiazepine-resistant SE [28]; in the near future it will hopefully provide useful results to inform clinical practice for the treatment of this challenging clinical condition.

Disclosures / Conflict of interest

Francesco Brigo has acted as a paid consultant to Eisai and LivaNova, and received travel support from Eisai. Eugen Trinka has acted as a paid consultant to Eisai, EVER Neuro Pharma, Biogen Idec, Medtronics, Bial, and UCB and has received speakers' honoraria from Bial, Eisai, Boehringer Ingelheim, Biogen, Newbridge, Novartis, and UCB Pharma in the past 3 years. Eugen Trinka has received research funding from UCB Pharma, Biogen, Novartis, Bayer, Eisai, Red Bull, Merck, the European Union, FWF Österreichischer Fond zur Wissenschaftsförderung, and Bundesministerium für Wissenschaft und Forschung. Eugen Trinka is also part of the investigators planning the ESET Trial and member of the Task Force on Classification of Status Epilepticus of the International League Against Epilepsy (ILAE). Other Authors have no conflict of interest.

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Table legends:

Table 1: Study design, definitions of SE and details of treatments in RCTs included

Table 2: Clinical characteristics of patients

Table 3. Ranking according to SUCRA and mean rank for the efficacy and safety outcomes

Table e-1: Risk of bias in included RCTs

Table e-2: Results of the pairwise meta-analyses for the efficacy and safety outcomes

Figure legends:

Figure 1: Study inclusion flow diagram

Figure 2: Network of treatment comparisons for efficacy and safety

Figure 3: Interval plots for the efficacy and safety outcomes

Supplementary material:

Appendix I: PRISMA checklist

Appendix II: Details of search strategy

Appendix III: Ranking according to SUCRA for the efficacy and safety outcomes

Table 1: Characteristics of included randomized controlled trials.

Study	Country	Definition(s) of status epilepticus	Participants and age	Details of benzodiazepine administration	Comparators	
Agarwal et al., 2007 [14]	India	Continuous convulsive seizure > 5 min without recovery of consciousness	Adults > 18 years	DZP 0.2 mg/kg at 2 mg/min IV, max 20 mg	PHT 20 mg/kg, max rate: 50 mg/min	VPA 20 mg/kg administered at 40 mg/min
Chen et al., 2011 [17]	China	≥2 seizures without full recovery of consciousness between seizures OR seizure > 5 min	Adults ≥ 15 years	DZP 0.2 mg/kg given twice at a 10-min interval	DZP 0.2 mg/kg at 5 mg/min and then infusion at 4 mg/h maintained for 3 min and then increased every 3 min by 1 lg/kg per min until SE control or maximum duration (1 h) of administration	VPA 30 mg/kg at 6 mg/kg per min followed by a continuous infusion at 1–2 mg/kg per h. Infusions maintained for at least 6 h after SE control and then gradually tapered over 24 h until eventually replaced by oral anticonvulsants
Chakravarthi et al., 2015 [15]	India	≥2 convulsive seizures without full recovery of consciousness between seizures OR continuous convulsive seizure > 5 min	Adolescents and adults	LZP 0.1 mg/kg at 1 mg/min IV	PHT 20 mg/kg with subsequent maintenance dose (not further specified), max rate: 50 mg/min	LEV 20 mg/kg administered at 100 mg/min with subsequent maintenance dose (not further specified)
Su et al., 2016 [18]	China	≥2 seizures without full recovery of consciousness between seizures OR seizure > 5 min	Adults ≥ 18 years	DZP 0.2 mg/kg given twice at a 10-min interval	PB 20 mg/kg (an additional 5–10 mg/kg could be administered) at 50 mg/min, followed by an intravenous dose of 100 mg every 6 h (maintained for 24–48 h and then gradually tapered replacement with oral AEDs, 24–72 h)	VPA 30 mg/kg (an additional 15 mg/kg could be administered) at 3 mg/kg/min, followed by continuous infusion at 1–2 mg/kg (maintained for 24–48 h and then gradually tapered replacement with oral AEDs, 24–72 h)
Misra et al., 2017 [16]	India	Convulsive SE: ≥2 convulsive seizures without full recovery or continuous convulsions > 5 min. Subtle convulsive SE: coma and ictal discharges on EEG and subtle convulsive movements	Adults > 18 years	LZP 4 mg in 2-4 min IV(repeated once if seizures not controlled)	VPA 30 mg/Kg at 100 mg/min	LCM 400 mg at 60 mg/min

DZP: diazepam
IV: intravenous
LCM: lacosamide
LZP: lorazepam
PB: phenobarbital
SE: status epilepticus
VPA: valproate

Table 2: Clinical characteristics of patients

Study	**No of patients, sex ratio (M:F)**	**Age Mean age±SD [range]**	**History of previous seizures**	**Type of SE**	**Seizure duration, Mean±SD [range]**	**Etiology of SE**
Agarwal et al., 2007 [14]	***PHT group***					
	50 32:18	27±15.1 years	NR	Convulsive SE (semiology not further specified) 100%	<2h in 52% of patients	AED withdrawal/noncompliance 28% Neurocysticercosis/tuberculoma 24% CNS infections 24% Primary generalized seizure 12% Stroke 4% Chronic renal failure 4% Eclampsia 4%
	VPA group					
	50 35:15	27.4±16.8 years	NR	Convulsive SE (semiology not further specified) 100%	<2h in 60% of patients	AED withdrawal/noncompliance 24% Neurocysticercosis/tuberculoma 24% CNS infections 20% Primary generalized seizure 16% Stroke 4% Extradural hematoma 4% Juvenile myoclonic epilepsy 4% Brain metastasis 4%
Chen et al., 2011 [17]	***DZP group***					
	36 20:16	41.14±18.67	NR	Generalized convulsive SE 100%	12 patients <4 h 12 patients 4-14 h 12 patients > 24 h	Epilepsy related 36% Viral encephalitis 28% Cerebrovascular disease 14% Others 22%
	VPA group					
	30 16:14	40.80±23.18	NR	Generalized convulsive SE 100%	11 patients <4 h 9 patients 4-14 h 10 patients > 24 h	Epilepsy related 33% Viral encephalitis 40% Cerebrovascular disease 17% Others 10%
Chakravarthi et al., 2015 [15]	***PHT group***					
	22 15:7	31.82±12.68 years	63.6%	Convulsive SE (semiology not further specified) 100%	72.05±48.57 min	Idiopathic 31.8% Acute symptomatic 13.6% Remote symptomatic 54.5%

	LEV group					
	22 12:10	39.00±18.40 years	77.2%	Convulsive SE (semiology not further specified) 100%	55.91±73.75 min	Idiopathic 27.3% Acute symptomatic 45.5% Remote symptomatic 27.3%
Su et al., 2016 [18]	***PB group***					
	37 19:18	37.14±14.98 years	NR	Generalized convulsive SE 100%	8 patients<4 h 29 patients>4 h	Epilepsy related 37.8% Viral encephalitis 37.8% Cerebrovascular disease 8.1% Others 16.2%
	VPA group					
	36 20/16	45.26±18.14 years	NR	Generalized convulsive SE 100%	10 patients<4 h 26 patients>4 h	Epilepsy related 25.08% Viral encephalitis 44.5% Cerebrovascular disease 8.3% Others 22.2%
Misra et al., 2017 [16]	***LCM group***					
	33 21:12	40 [18-90]		Generalized convulsive SE 90.9% Subtle convulsive SE 9.1%	2 hours (median) [0.08-160]	CNS infections 33.3% Stroke 30.3% Othrs 36.4%
	VPA group					
	33 25:8	40 [18-85]		Generalized convulsive SE 97% Subtle convulsive SE 3%	2 hours (median) [0.08-60]	CNS infections 33.3% Stroke 18.2% Others 48.5%

AED: antiepileptic drugs

CNS: central nervous system

h: hour(s)

min: minute(s)

NR: not explicitly reported

SD: standard deviation

SE: status epilepticus

Table 3. Ranking according to SUCRA and mean rank for the efficacy and safety outcomes

a) Status epilepticus cessation

Treatment	SUCRA	Mean rank
PHT	36.8	4.3
VPA	34.1	4.3
DZP	47.2	3.6
LEV	65.9	2.7
PHB	79.2	2.0
LCM	44.2	3.8

b) Seizure freedom at 24 hours

Treatment	SUCRA	Mean rank
PHT	53.8	3.3
VPA	51.1	3.4
DZP	52.7	3.4
LEV	22.1	4.9
PHB	94.9	1.3
LCM	25.4	4.7

c) Respiratory depression

Treatment	SUCRA	Mean rank
PHT	34.0	4.3
VPA	77.8	2.1
DZP	40.8	4.0
LEV	52.3	3.4
PHB	18.4	5.1
LCM	76.7	2.2

d) Hypotension

Treatment	SUCRA	Mean rank

PHT	20.7	4.2
VPA	74.8	2.0
DZP	42.6	3.3
PHB	23.6	4.1
LCM	88.3	1.5

Abbreviations: DZP=diazepam, LCM=lacosamide, LEV=levetiracetam, PHB=phenobarbital, PHT=phenytoin, SUCRA=surface under the cumulative ranking curve, VPA=valproic acid. Higher SUCRA values correspond to higher probabilities of better efficacy/tolerability.

Table 4: Efficacy outcomes of included RCTs (direct comparisons)

Study	**SE cessation within 1 hour of drug administration**			**Seizure freedom at 24 hours**		
	Comparators		***Statistical difference***	***Comparators***		***Statistical difference***
Agarwal et al., 2007 [14]	***PHT***	***VPA***		***PHT***	***VPA***	
	42/50	44/50	P=0.773	50/50	50/50	P=1
Chen et al., 2011 [17]	***DZP***	***VPA***		***DZP***	***VPA***	
	20/36	15/30	P=0.652	15/36	12/30	P=0.93
Chakravarthi et al., 2015 [15]	***PHT***	***LEV***		***PHT***	***LEV***	
	15/22	13/22	P=0.53	9/22	4/22	P=0.18
Su et al., 2016 [18]	***PB***	***VPA***		***PB***	***VPA***	
	30/37	16/36	P=0.001	28/37	11/36	P<0.0001
Misra et al., 2017 [16]	***LCM***	***VPA***		***LCM***	***VPA***	
	21/33	23/33	P=0.79	15/33	20/33	P=0.29

AED: antiepileptic drugs

LCM: lacosamide

LEV: levetiracetam

NR: not explicitly reported

PHT: phenytoin

SE: status epilepticus

VPA: valproic acid

Table e-1: Risk of bias in included randomized controlled trials

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Agarwal et al., 2007 [14]	Unclear risk (not described)	Unclear risk (not described)	Unclear risk (not described)	Low risk (outcome measurement unlikely to be influenced by lack of blinding)	Low risk (no missing outcome data)	Unclear risk (insufficient information to permit judgement)
Chen et al., 2011 [17]	Low risk (use of table of random digits)	Unclear risk (not described)	High risk (no blinding)	Low risk (outcome measurement unlikely to be influenced by lack of blinding)	Low risk (no missing outcome data)	Unclear risk (insufficient information to permit judgement)
Chakravarthi et al., 2015 [15]	High risk (Sequence generation depending on the order of recruitment)	High risk (open random allocation schedule)	High risk (no blinding)	Low risk (outcome measurement unlikely to be influenced by lack of blinding)	Low risk (no missing outcome data)	Unclear risk (insufficient information to permit judgement)
Su et al., 2016 [18]	Low risk (use of table of random digits)	Low risk	High risk (no blinding)	Low risk (outcome measurement unlikely to be influenced by lack of blinding)	Low risk (no missing outcome data)	Unclear risk (insufficient information to permit judgement)
Misra et al., 2017 [16]	Low risk (use of computer-generated random numbers)	Unclear risk (not described)	High risk (no blinding)	Low risk (outcome measurement unlikely to be influenced by lack of blinding)	Low risk (no missing outcome data)	Unclear risk (insufficient information to permit judgement)

Table e-2. Results of the pairwise meta-analyses for the efficacy and safety outcomes

a) Status epilepticus cessation

Comparisons	Number of studies	Number of participants allocated to any arm	Odds Ratio (95% CI)	p value
VPA vs. PHT	1	50, 50	1.40 (0.45-4.37)	0.566
LEV vs. PHT	1	22, 22	0.67 (0.20-2.32)	0.532
DZP vs. VPA	1	36, 30	1.25 (0.47-3.30)	0.653
LCM vs. VPA	1	33, 30	0.76 (0.27-2.12)	0.602
PHB vs. VPA	1	37, 36	5.36 (1.87-15.36)	0.002

b) Seizure freedom at 24 hours

Comparisons	Number of studies	Number of participants allocated to any arm	Odds Ratio (95% CI)	p value
VPA vs. PHT	1	50, 50	1.00 (0.02-51.38)	1.000
LEV vs. PHT	1	22, 22	0.32 (0.08-1.27)	0.106
DZP vs. VPA	1	36, 30	1.07 (0.40-2.87)	0.891
LCM vs. VPA	1	33, 30	0.54 (0.20-1.44)	0.219
PHB vs. VPA	1	37, 36	7.07 (2.52-19.86)	<0.001

c) Respiratory depression

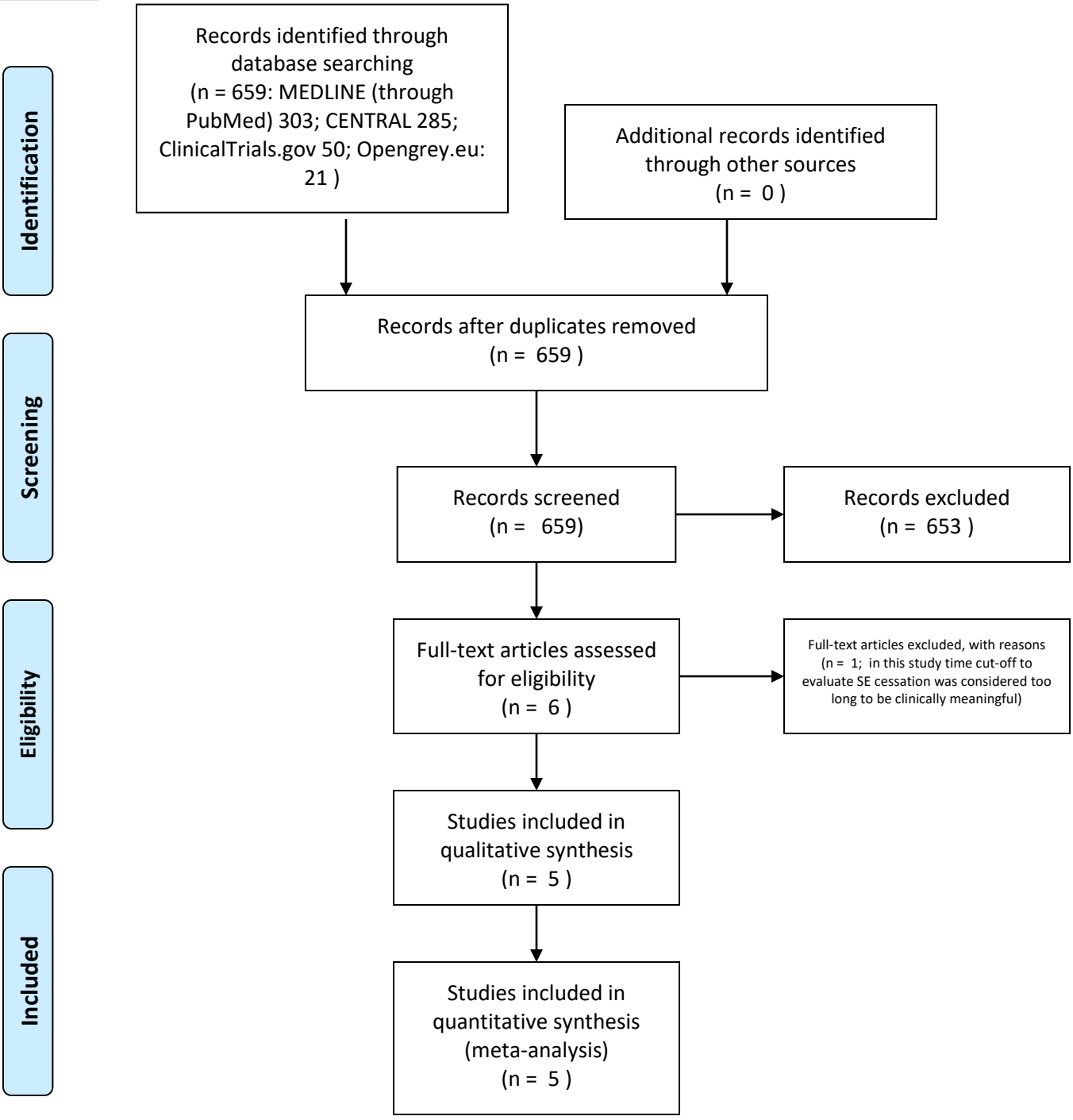
Comparisons	Number of studies	Number of participants allocated to any arm	Odds Ratio (95% CI)	p value
VPA vs. PHT	1	50, 50	0.19(0.01-4.10)	0.291
LEV vs. PHT	1	22, 22	0.59 (0.14-2.48)	0.474
DZP vs. VPA	1	36, 30	4.42 (0.20-95.72)	0.344
LCM vs. VPA	1	33, 30	1.00 (0.38-2.63)	1.000
PHB vs. VPA	1	37, 36	15.06 (0.82-278.09)	0.068

d) Hypotension

Comparisons	Number of studies	Number of participants allocated to any arm	Odds Ratio (95% CI)	p value
VPA vs. PHT	1	50, 50	0.07 (0.00-1.24)	0.069
DZP vs. VPA	1	36, 30	4.42 (0.20-95.72)	0.344
LCM vs. VPA	1	33, 30	0.32 (0.01-8.23)	0.494
PHB vs. VPA	1	37, 36	12.35 (0.68-232.15)	0.093

Abbreviations: CI=confidence interval, DZP=diazepam, LCM=lacosamide, LEV=levetiracetam, PHB=phenobarbital, PHT=phenytoin, VPA=valproic acid.

PRISMA 2009 Flow Diagram

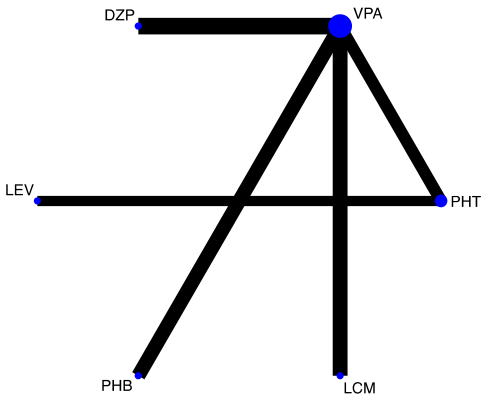


From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

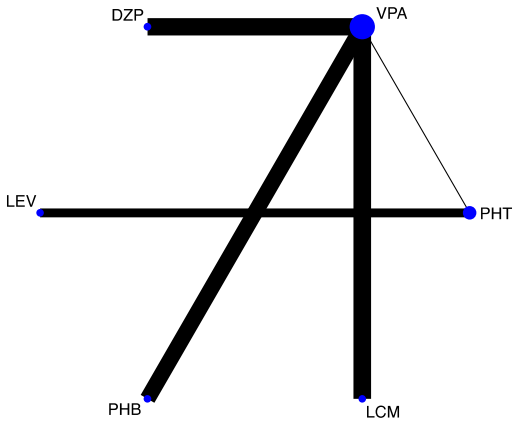
For more information, visit www.prisma-statement.org.

Figure 2. Network of treatment comparisons for efficacy and safety

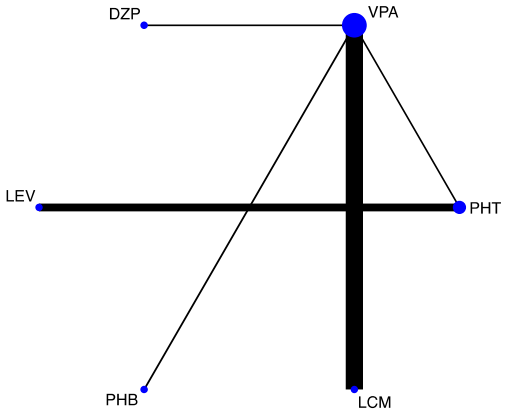
a) Status epilepticus cessation



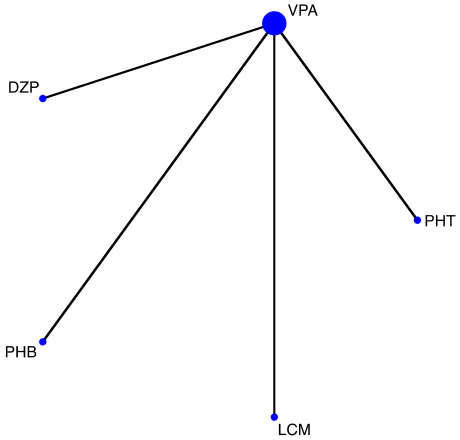
b) Seizure freedom at 24 hours



c) Respiratory depression



d) Hypotension

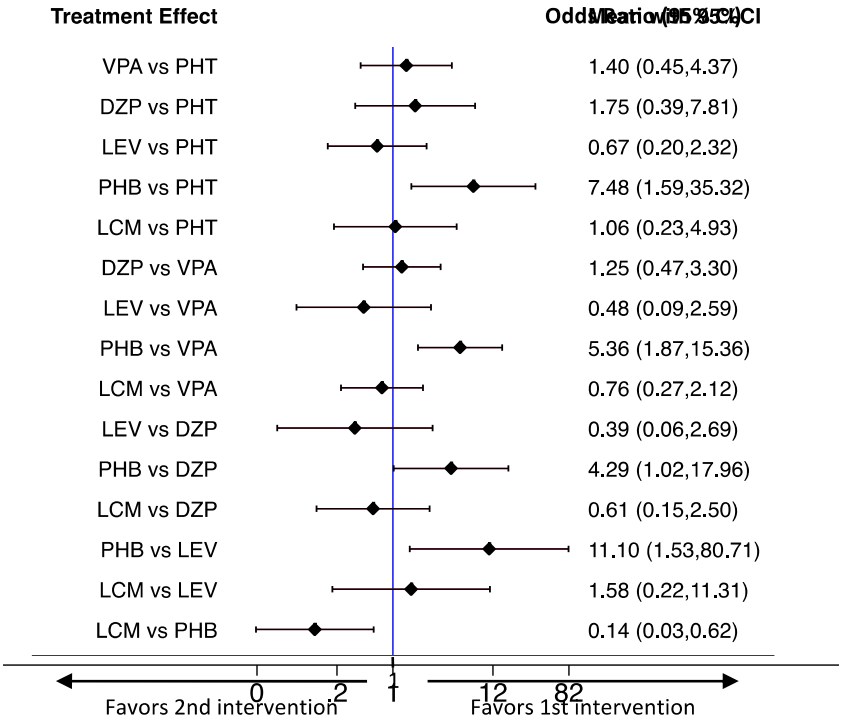


The width of the lines is proportional to the inverse of the variance of the comparison treatment effect and the size of every circle is proportional to the number of randomly assigned participants.

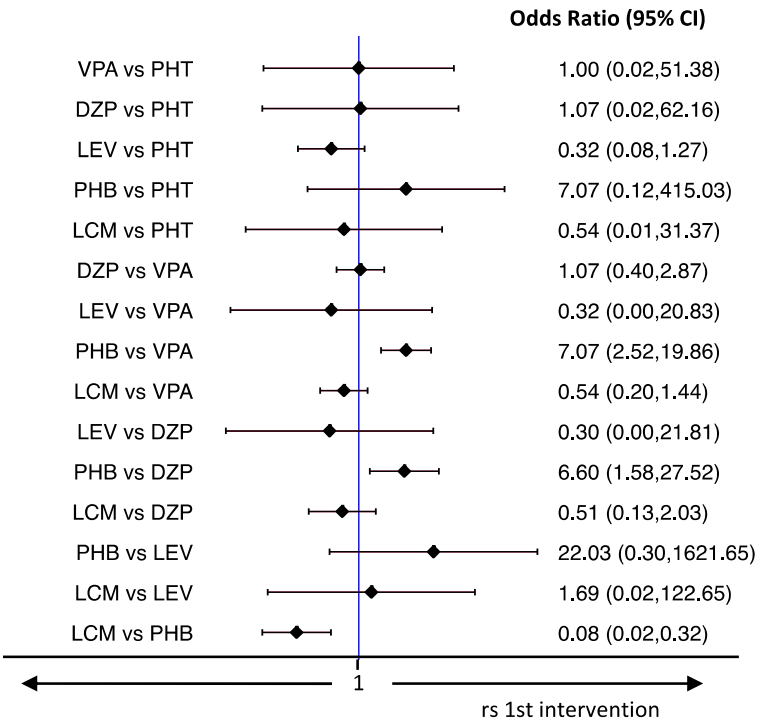
Abbreviations: DZP=diazepam, LCM=lacosamide, LEV=levetiracetam, PHB=phenobarbital, PHT=phenytoin, VPA=valproic acid.

Figure 3. Interval plots for the efficacy and safety outcomes

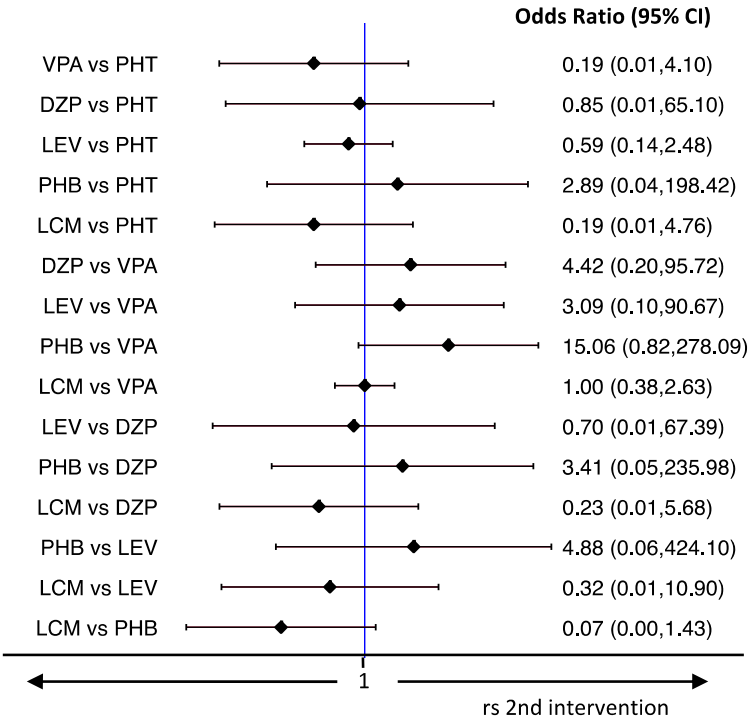
a) Status epilepticus cessation



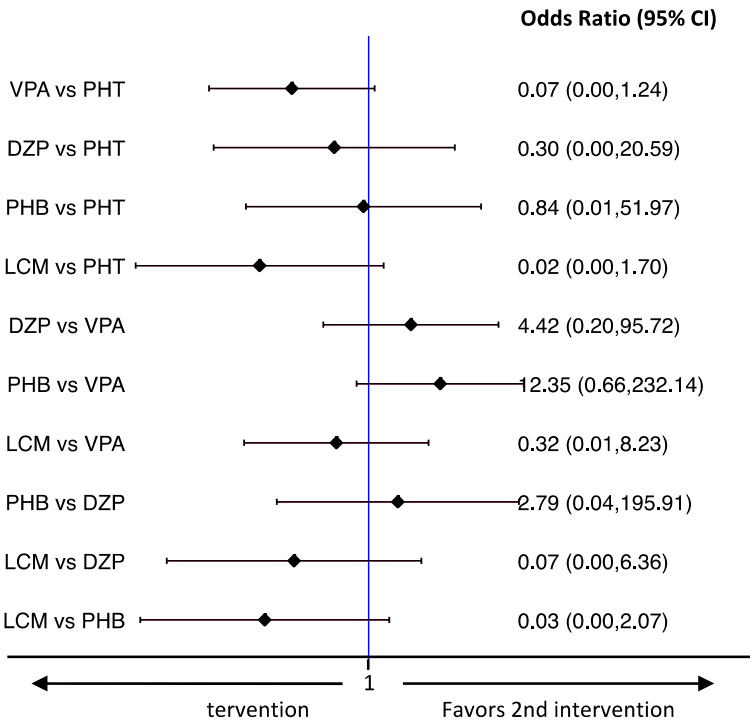
b) Seizure freedom at 24 hours



c) Respiratory depression



d) Hypotension



Abbreviations: CI=confidence interval, DZP=diazepam, LCM=lacosamide, LEV=levetiracetam, PHB=phenobarbital, PHT=phenytoin, VPA=valproic acid.

Highlights

- PHB was superior to PHT, VPA, DZP, LEV and LCM with respect to SE cessation
- PHB performed better than VPA, DZP and LCM in seizure freedom at 24 hours
- No differences in the occurrence of respiratory depression and hypotension
- High-dose PHB is effective in controlling SE and preventing seizure recurrence
- LCM and VPA could be better tolerated options